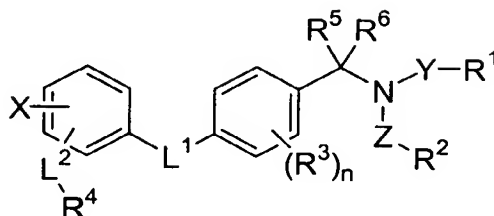


We claim:

1. A compound of the formula



5

or a pharmaceutically acceptable salt or solvate thereof; wherein:

R^1 is selected from the group consisting of H, alkyl, haloC₁-C₆ alkyl, cycloalkyl, cycloalkylNH-, arylalkyl, heterocycloalkyl, heteroaryl, -N(R²)₂, -N(R²)aryl, unsubstituted
10 aryl and aryl substituted with one to three X, wherein each R² can be the same or different and is independently selected when there are more than one R² present;

R^2 is selected from the group consisting of H and C₁-C₆ alkyl;

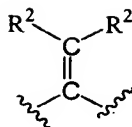
R^3 is 1-3 substituents selected from the group consisting of H, C₁-C₆ alkyl, Cl, F, CF₃, OCF₂H, OCF₃, OH and C₁-C₆ alkoxy, wherein R³ can be the same or different
15 and is independently selected when there are more than one R³ present;


R^4 is selected from the group consisting of H, C₁-C₆ alkyl, C₁-C₆ alkoxy, cycloalkyl, alkenyl, aryl, benzyl, heteroaryl, heterocycloalkyl, arylNH-, heteroarylNH-, cycloalkylNH-, N(R²)₂, or N(R²)aryl, said alkyl, alkoxy, cycloalkyl, alkenyl, phenyl, pyridine-N-oxide and heteroaryl optionally substituted with one to three X, wherein X
20 can be the same or different and is independently selected when there are more than one X present;

R^5 is H or C₁-C₆ alkyl;

R^6 is H or C₁-C₆ alkyl; or

R^5 and R^6 taken together with the carbon atom to which they are attached form
25 a carbonyl group;

L^1 is , $-C(R^2)_2-$, $-C(O)-$, $-CHOR^2-$, $-C=NOR^5-$, $-SO_2-$, $-SO-$, $-S-$, $-O-$, $-N(R^2)-$, $-C(O)NR^2-$, $-N(R^2)C(O)-$, $-CHCF_2-$ or $-CF_2-$;

L^2 is a covalent bond, C_1 - C_6 alkylene, $-C(R^2)_2-$, , $-CHOR^2-$, $-C(R^2)OH$, $-C=NOR^5-$, $-SO_2-$, $-N(R^2)SO_2-$, $-SO-$, $-S-$, $-O-$, $-SO_2N(R^2)-$, $-N(R^2)_2-$, $-C(O)N(R^2)-$ or $-N(R^2)C(O)-$;

X is selected from the group consisting of H, halogen, CF_3 , CN, OCF_2H , OCF_2CF_3 , OCF_3 , OR^2 , C_1 - C_6 alkyl, cycloalkyl, cycloalkoxy, C_1 - C_6 alkoxy, alkoxy C_1 - C_6 alkoxy, O-cycloalkyl, cycloalkylamino, cycloalkylalkoxy, heteroalkyl, $-OSO_2R^2$, $-COOR^2$, $-CON(R^2)_2$, $N(R^2)_2$, and NR^2 aryl, wherein X can be the same or different, and is independently selected when there are more than one X present;

Y is a covalent bond, $-CH_2-$, $-SO_2-$, or $-C(O)-$;

Z is a covalent bond, $-CH_2-$, $-SO_2-$ or $-C(O)-$; or

Y , R^1 , Z and R^2 can be taken together with the nitrogen atom to which they are attached to form a heterocycloalkyl; with the following provisos:

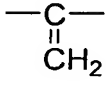
L^2 and R^4 , when taken together, cannot have two heteroatoms covalently bonded together;

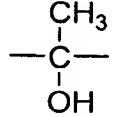
when R^2 is H, Z cannot be $-S(O)-$, $-SO_2-$, or $-C(O)-$; and

when Y is a covalent bond, R^1 cannot form a N-N bond with the nitrogen atom.

2. A compound according to claim 1 wherein

L^1 is $-SO_2-$, $-CH_2-$, $-CHCH_3-$, $-C(O)-$, $-C=NOR^5-$, $-C(CH_3)_2-$, $-CHOH-$, $-O-$, $-S-$ or $-S(O)-$;

L^2 is $-SO_2-$, $-C(O)-$, $-CH_2-$, $-CH(CH_3)-$, $-C(CH_3)_2-$, , $-NH-$, $-O-$,

$-NHSO_2-$, $-NHC(O)-$, or  ;

R¹ is H, -CH₃NH₂, -CH₂CF₃, -NHC₃H₇, -NHC₂H₆, -NHC₄H₉, C₁-C₆ alkyl, -CF₃, -CH(CH₂)₂, thiophenyl, morpholinyl, cyclopropyl, benzyl, naphthyl, -C(CH₃)₃, NHphenyl, 3,5-difluorophenyl, phenyl, N-cyclopentyl or N(CH₃)₂;

R² is H or CH₃;

5 R³ is OH;

R⁴ is furanyl, pyridyl, pyrimidyl, thiophenyl, quinolyl, t-butoxy, alkoxy, cyclohexyl, phenyl, tolyl, C₃H₇, pyrimidyl, methoxyphenyl, morpholinylphenyl or CH₃; with the proviso that when R⁴ is t-butoxy, L² must be -C(O)-, -CH₂-,

-CHCH₃-, -C(CH₃)₂- or $\begin{array}{c} \text{---C---} \\ || \\ \text{CH}_2 \end{array}$, all of the above optionally substituted with one
10 to three X, wherein X can be the same or different and are independently selected when there are more than one X present;

R⁵ and R⁶ are independently H or CH₃;

Y is a covalent bond, -SO₂- or -C(O)-;

Z is a covalent bond; or

15 R¹, Y, R² and Z taken together with the nitrogen atom form a morpholinyl group.

3. The compound according to claim 2 wherein

20 X is halogen, OH, or cyclopropyl;

R³ is OH;

R⁵ and R⁶ are independently H or CH₃;

X is H, halogen, CF₃, OCH₃, OH, OCF₃, OCF₂H, CH₃ or C₁-C₆ cycloalkyl;

Y is a covalent bond;

25 Z is -SO₂- or -C(O)-;

L¹ is -SO₂- or -CH₂-;

L² is -SO₂-;

R¹ is CH₃ or CF₃; and

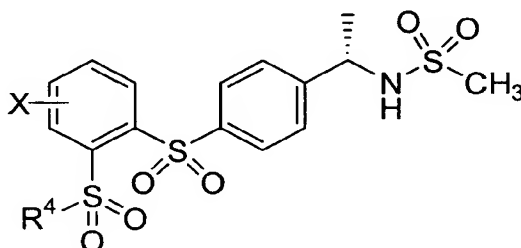
R⁴ is phenyl, pyrimidyl or pyridyl, said phenyl, pyrimidyl or pyridyl groups
30 optionally substituted with one to three substituents selected from the group consisting of C₁-C₆ alkyl, C₁-C₆ alkoxy, OH, CF₃ and halogen, wherein said substituents can be

the same or different and are independently selected when there are more than one substituent.

4. The compound according to claim 3 wherein the phenyl in R⁴ is substituted with OCH₃ or halogen.

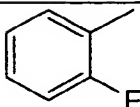
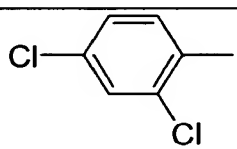
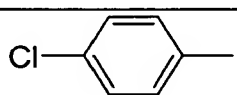
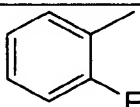
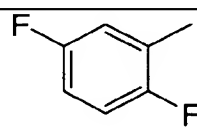
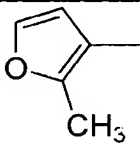
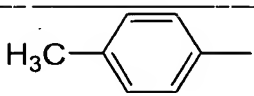
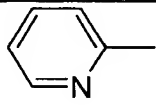
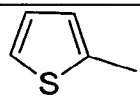
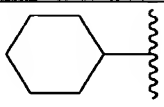
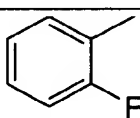
5. The compound according to claim 4 wherein the halogen is selected from fluorine and chlorine.

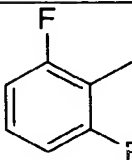
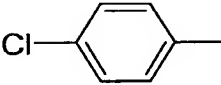
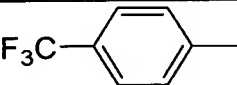
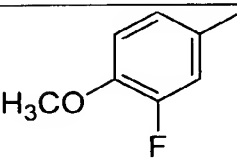
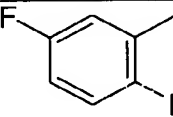
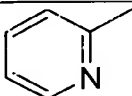
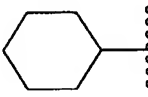
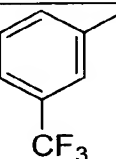
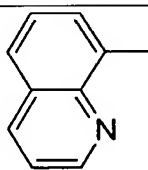
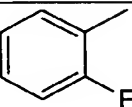
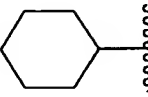
6. The compound according to Claim 1 of the formula

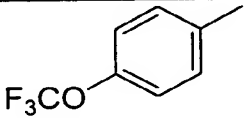
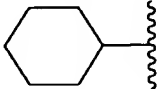
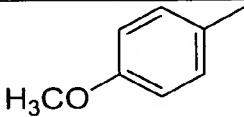
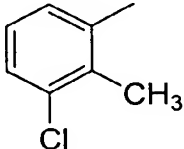
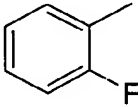
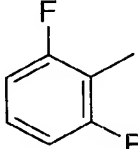
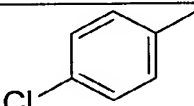
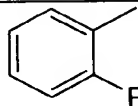
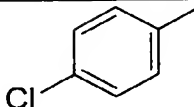
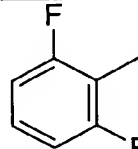
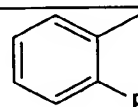


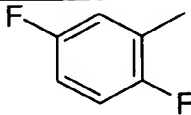
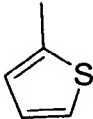
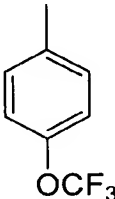
or a pharmaceutically acceptable salt or solvate thereof, wherein X and R⁴ are as shown in the table below:

Example	X	R ⁴
A	OCH ₃	
B	OCH ₃	
C	OCF ₂ H	
F	OCH ₃	

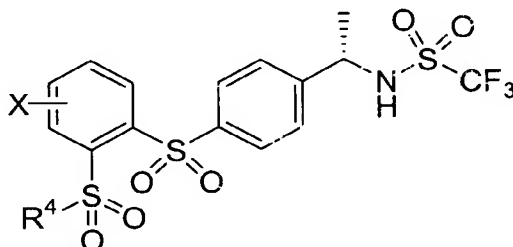
Example	X	R ⁴
G	CH ₃	
I	OCH ₃	
J	OCF ₃	
L	Cl	
O	Cl	
P	OCH ₃	
Q	CH ₃	
T	Cl	
U	OCH ₃	
Z	OCH ₃	
AA	OCH ₃	C ₃ H ₇
AB	CF ₃	

Example	X	R ⁴
AC	CF ₃	
AF	CF ₃	
AI	CF ₃	
AK	Cl	
AM	Cl	
AO	Cl	
AQ	Cl	
AU	Cl	
AV	Cl	
AX	Cl	C ₃ H ₇
BA	OCF ₃	
BB	OCF ₃	

Example	X	R ⁴
BC	OCF ₃	
BG	OCH ₃	
BX	OCH ₃	
CB	CH ₃	
CD	Cl	
CE	Cl	
CW	OH	
CX	OH	
DA	OCF ₂ H	
FR	H	
FS	H	

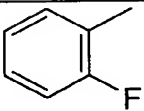
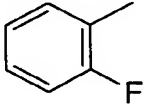
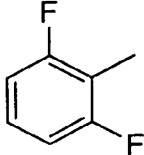
Example	X	R ⁴
FT	H	
FV	H	
FW	H	

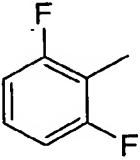
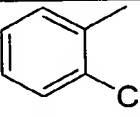
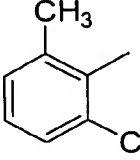
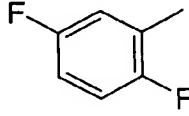
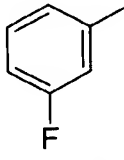
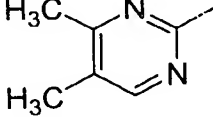
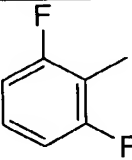
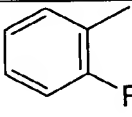
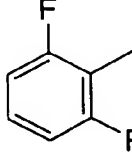
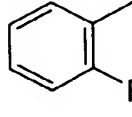
7. The compound according to Claim 1 of the formula

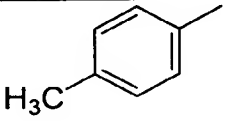
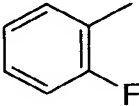
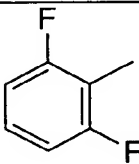
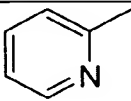
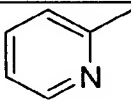
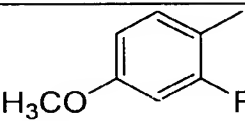
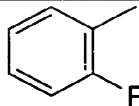
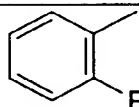
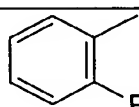
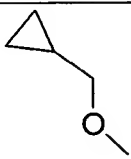
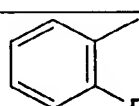


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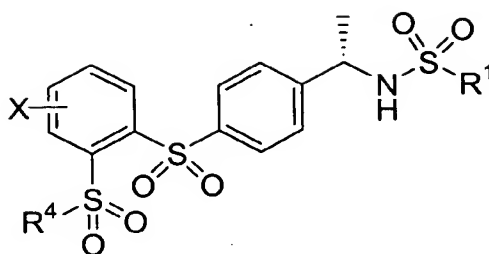
or a pharmaceutically acceptable salt or solvate thereof,
wherein X and R⁴ are as shown in the table below:

Example	X	R ⁴
R	CF ₃	
S	Cl	
W	Cl	

AE	CF ₃	
AG	CF ₃	
AH	CF ₃	
AR	Cl	
AS	Cl	
AW	Cl	
AZ	Cl	
BD	OCF ₃	
BJ	OCH ₃	
BZ	CH ₃	

CA	CH ₃	
FY	H	
FZ	H	
GG	Cl	
GH	CF ₃	
GI	Cl	
GJ	OCH ₃	
GL	OH	
GM	OCH(CH ₃) ₂	
GN		

8. The compound according to Claim 1 of the formula

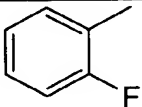
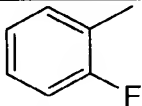
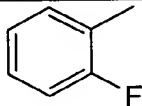
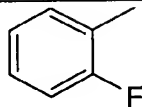
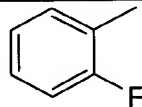
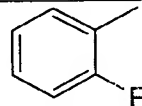
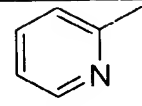
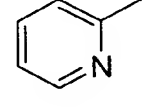

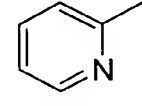

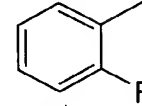

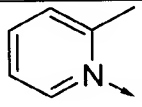
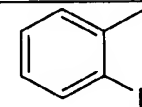


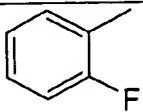
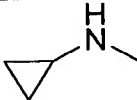
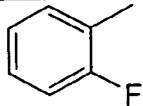
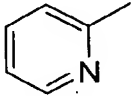
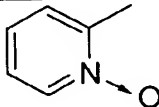
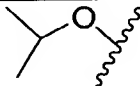
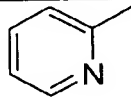
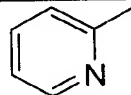
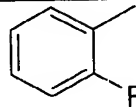
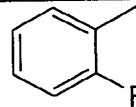
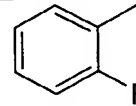
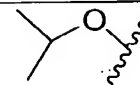
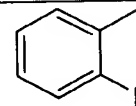
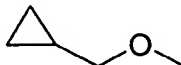
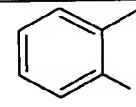
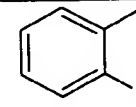
or a pharmaceutically acceptable salt or solvate thereof;

wherein X, R¹ and R⁴ are as shown in the table below:

5

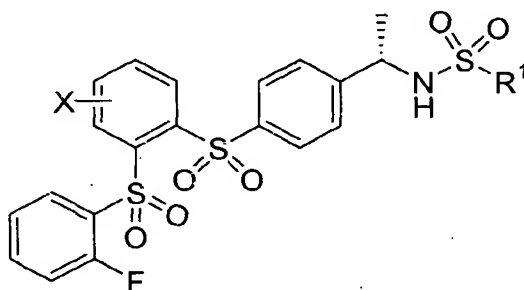
Example	X	R ¹	R ⁴
A	OCH ₃	CH ₃	
C	OCF ₂ H	CH ₃	
G	CH ₃	CH ₃	
L	Cl	CH ₃	
R	CF ₃	CF ₃	
S	Cl	CF ₃	
AB	CF ₃	CH ₃	
AT	Cl	N(CH ₃) ₂	

Example	X	R ¹	R ⁴
BA	OCF ₃	CH ₃	
BD	OCF ₃	CF ₃	
BZ	CH ₃	CF ₃	
CD	Cl	CH ₃	
FS	H	CH ₃	
FY	H	CF ₃	
GG	Cl	CF ₃	
GH	CF ₃	CF ₃	
XXIX		CF ₃	
XXX		CF ₃	
XXXI		CF ₃	
XXXII	CN	CF ₃	

Example	X	R ¹	R ⁴
XXXIII	NH ₂	CF ₃	
XXXIV		CF ₃	
XXXV	Cl	CF ₃	
XXXVI	Cl	CF ₃	
XXXVII		CF ₃	
XXXVIII	CN	CF ₃	
XXXIX	-CONH ₂	CF ₃	
XXXX	-OCH ₃	CF ₃	
XXXXI	-OH	CF ₃	
XXXXII		CF ₃	
XXXXIII		CF ₃	
XXXXIV	H ₃ C-CH ₂ -O-	CF ₃	

Example	X	R ¹	R ⁴
XXXXV		CF ₃	
XXXXXV	OCH ₃	CF ₃	
XXXXXXVI		CH ₃	

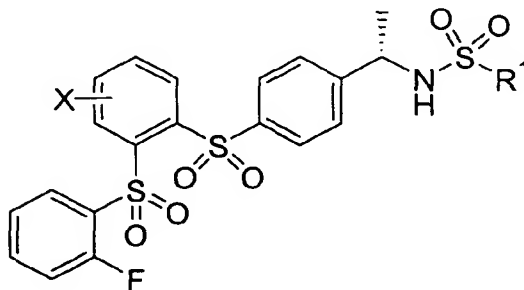
9. The compound according to Claim 1 of the formula



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or a pharmaceutically acceptable salt or solvate thereof, wherein X is OCH₃ and R¹ is CH₃.

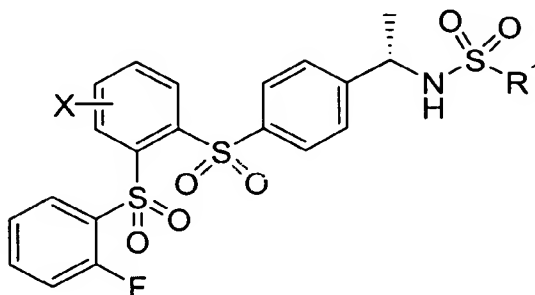
10. The compound according to Claim 1 of the formula



10

or a pharmaceutically acceptable salt or solvate thereof, wherein X is OCF₂H and R¹ is CH₃.

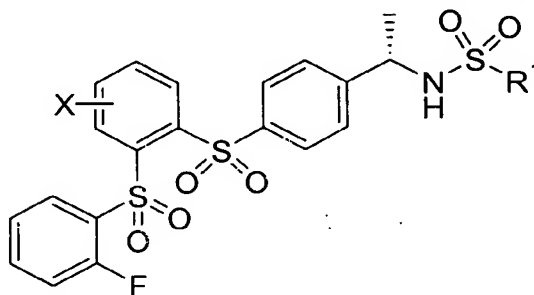
11. The compound according to Claim 1 of the formula



or a pharmaceutically acceptable salt or solvate thereof, wherein X is CH₃ and R¹ is

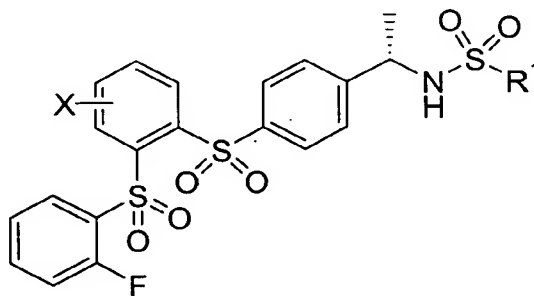
5 CH₃.

12. The compound according to Claim 1 of the formula



10 or a pharmaceutically acceptable salt or solvate thereof, wherein X is Cl and R¹ is CH₃.

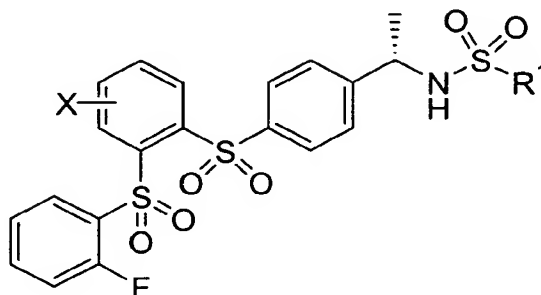
13. The compound according to Claim 1 of the formula



15

or a pharmaceutically acceptable salt or solvate thereof, wherein X is CF₃ and R¹ is CF₃.

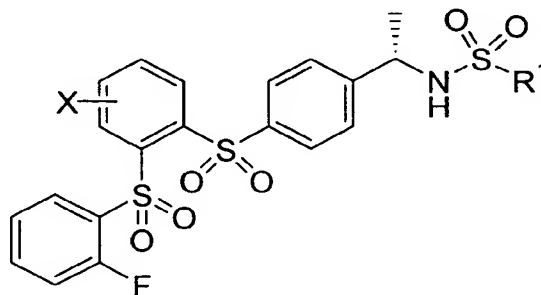
14. The compound according to Claim 1 of the formula



or a pharmaceutically acceptable salt or solvate thereof, wherein X is Cl and R¹ is CF₃.

5

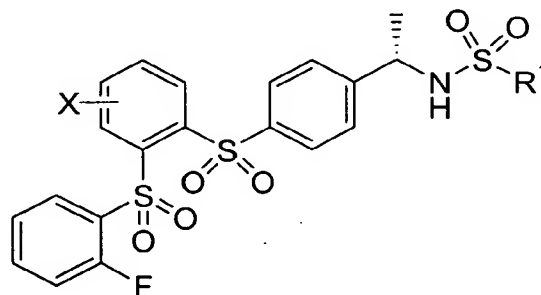
15. The compound according to Claim 1 of the formula



or a pharmaceutically acceptable salt or solvate thereof; wherein X is CF₃ and R¹ is CH₃.

10

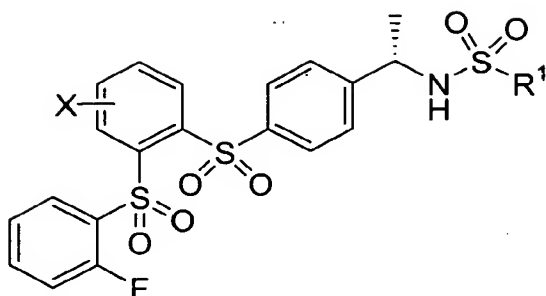
16. The compound according to Claim 1 of the formula



or a pharmaceutically acceptable salt or solvate thereof, wherein X is Cl and R¹ is

15 N(CH₃)₂.

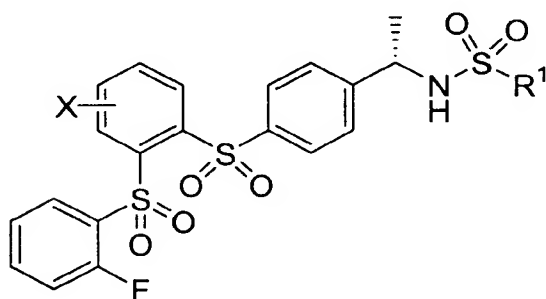
17. The compound according to Claim 1 of the formula



or a pharmaceutically acceptable salt or solvate thereof, wherein X is OCF_3 and R^1 is CH_3 .

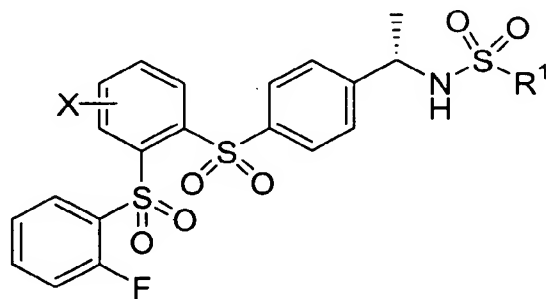
5

18. The compound according to Claim 1 of the formula



10 or a pharmaceutically acceptable salt or solvate thereof, wherein X is OCF_3 and R^1 is CF_3 .

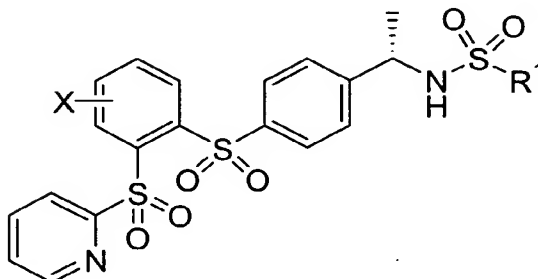
19. The compound according to Claim 1 of the formula



15

or a pharmaceutically acceptable salt or solvate thereof, wherein X is CH_3 and R^1 is CF_3 .

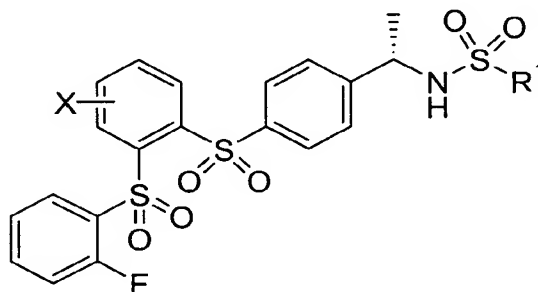
20. The compound according to Claim 1 of the formula



5

or a pharmaceutically acceptable salt or solvate thereof, wherein X is cyclopropyl and R¹ is CF₃.

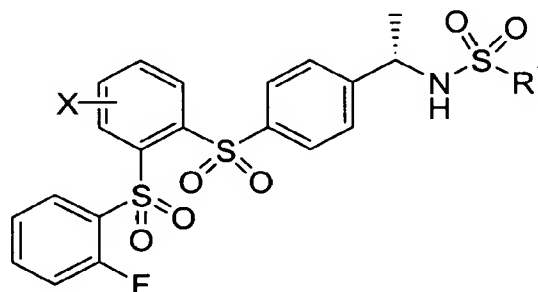
21. The compound according to Claim 1 of the formula



10

or a pharmaceutically acceptable salt or solvate thereof, wherein X is H and R¹ is CH₃.

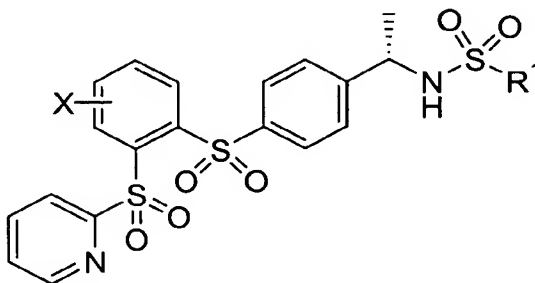
22. The compound according to Claim 1 of the formula



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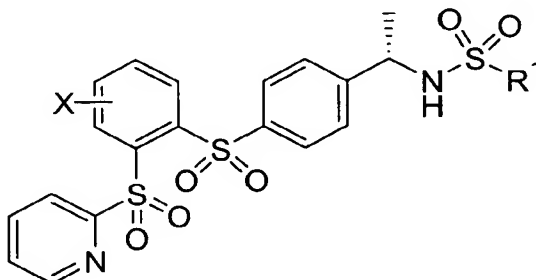
or a pharmaceutically acceptable salt or solvate thereof, wherein X is H and R¹ is CF₃.

23. The compound according to Claim 1 of the formula



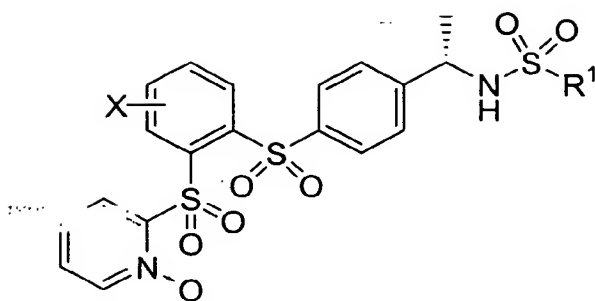
or a pharmaceutically acceptable salt or solvate thereof, wherein X is Cl and R¹ is CF₃.

24. The compound according to Claim 1 of the formula



or a pharmaceutically acceptable salt or solvate thereof, wherein X is CF₃ and R¹ is CF₃.

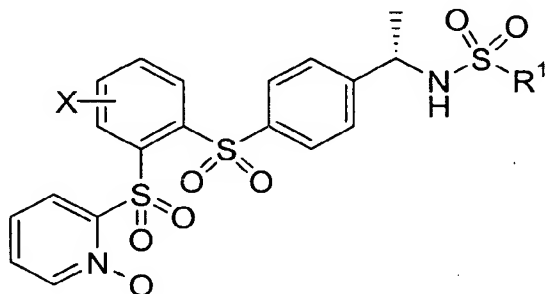
25. The compound according to Claim 1 of the formula



or a pharmaceutically acceptable salt or solvate thereof, wherein X is cyclopropyl and R¹ is CF₃.

5

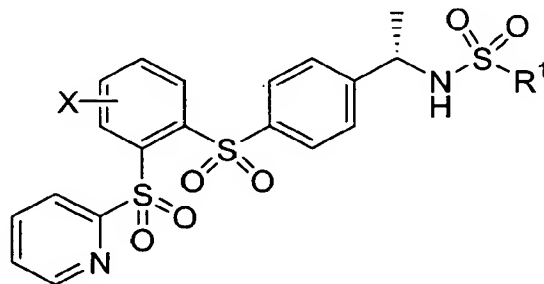
26. The compound according to Claim 1 of the formula



10

or a pharmaceutically acceptable salt or solvate thereof, wherein X is Cl and R¹ is CF₃.

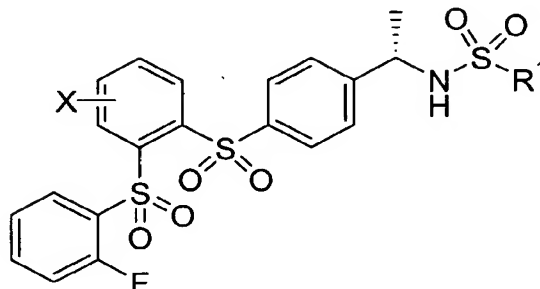
27. The compound according to Claim 1 of the formula



15

or a pharmaceutically acceptable salt or solvate thereof, wherein X is cyclopropyl and R¹ is CH₃.

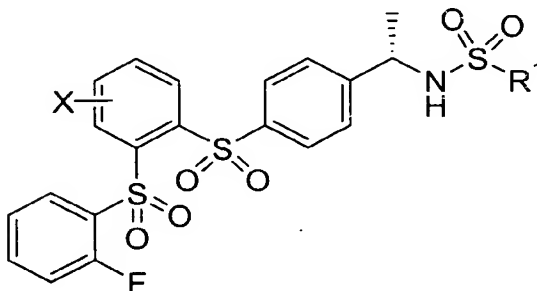
28. The compound according to Claim 1 of the formula



5

or a pharmaceutically acceptable salt or solvate thereof, wherein X is cyclopropyl and R¹ is CF₃.

29. The compound according to Claim 1 of the formula



10

or a pharmaceutically acceptable salt or solvate thereof, wherein X is cyclopropyl and R¹ is CH₃.

15

30. A pharmaceutical composition comprising one or more compounds according to claim 1 and one or more pharmaceutically acceptable carriers.

31. A pharmaceutical composition comprising one or more compounds according to claim 7 and one or more pharmaceutically acceptable carriers.

20

32. A method of stimulating cannabinoid CB₂ receptors in a patient comprising administering to said patient having CB₂ receptors an effective CB₂ receptor stimulating amount of one or more compounds according to Claim 1.

5 33. A method of treating cancer, inflammatory diseases, immunomodulatory diseases, or respiratory diseases comprising administering to a patient in need of such treatment one or more compounds according to claim 1.

10 34. A method of treating cutaneous T cell lymphoma, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, glaucoma, diabetes, sepsis, shock, sarcoidosis, idiopathic pulmonary fibrosis, bronchopulmonary dysplasia, retinal disease, scleroderma, osteoporosis, renal ischemia, myocardial infarction, cerebral stroke, cerebral ischemia, nephritis, hepatitis, glomerulonephritis, cryptogenic fibrosing alveolitis, psoriasis, atopic dermatitis, vasculitis, allergy,
15 seasonal allergic rhinitis, Crohn's disease, inflammatory bowel disease, reversible airway obstruction, adult respiratory distress syndrome, asthma, chronic obstructive pulmonary disease (COPD), bronchitis, colitis, coronary artery disease, melanoma, transplant rejection, graft versus host disease, Hashimoto's thyroiditis, Graves disease, myasthenia gravis or Goodpasture's syndrome comprising administering to a
20 patient in need of such treatment a compound according to claim 1.

25 35. The method of claim 32 wherein the condition or disease treated is selected from rheumatoid arthritis, multiple sclerosis, seasonal allergic rhinitis and chronic obstructive pulmonary disease.

36. A pharmaceutical composition made by combining one or more compounds of Claim 1 and one or more pharmaceutically acceptable carriers.

30 37. A process for making a pharmaceutical composition comprising combining one or more compounds of Claim 1 and one or more pharmaceutically acceptable carriers.

38. A method of treating rheumatoid arthritis which comprises co-administration one or more compounds selected from the class consisting of a COX-2 inhibitor, a COX-1 inhibitor, an immunosuppressive, a steroid, an anti-TNF- α compound or other classes of compounds indicated for the treatment of rheumatoid arthritis and one or more compounds of Claim 1.

39. A method of treating rheumatoid arthritis which comprises co-administration one or more compounds selected from the class consisting of a COX-2 inhibitor, a COX-1 inhibitor, an immunosuppressive, a steroid, an anti-TNF- α compound, a PDE IV inhibitor or other classes of compounds indicated for the treatment of rheumatoid arthritis and one or more compounds of Claim 7.

40. The method of Claim 38 wherein the COX-2 inhibitor is Celebrex or Vioxx, the COX-1 inhibitor is Feldene, the immunosuppressive is methotrexate, leflunimide, sulfasalazine or cyclosporin, the steroid is β -methasone and the anti-TNF- α compound is Enbrel or Remicade.

41. The method of Claim 39 wherein the COX-2 inhibitor is Celebrex or Vioxx, the COX-1 inhibitor is Feldene, the immunosuppressive is methotrexate, leflunimide, sulfasalazine or cyclosporin, the steroid is β -methasone and the anti-TNF- α compound is Enbrel or Remicade.

42. A composition for treating rheumatoid arthritis which comprises one or more compounds selected from the class consisting of a COX-2 inhibitor, a COX-1 inhibitor, an immunosuppressive, a steroid, an anti-TNF- α compound or other classes of compounds indicated for the treatment of rheumatoid arthritis and one or more compounds of Claim 1.

43. A composition for treating rheumatoid arthritis which comprises one or more compounds selected from the class consisting of a COX-2 inhibitor, a COX-1 inhibitor, an immunosuppressive, a steroid, an anti-TNF- α compound or other classes of compounds indicated for the treatment of rheumatoid arthritis and one or more compounds of Claim 7.

44. The composition of Claim 42 wherein the COX-2 inhibitor is Celebrex or Vioxx, the COX-1 inhibitor is Feldene, the immunosuppressive is methotrexate, leflunimide, sulfasalazine or cyclosporin, the steroid is β -methasone
5 and the anti-TNF- α compound is Enbrel or Remicade.

45. The composition of Claim 43 wherein the COX-2 inhibitor is Celebrex or Vioxx, the COX-1 inhibitor is Feldene, the immunosuppressive is methotrexate, leflunimide, sulfasalazine or cyclosporin, the steroid is β -methasone
10 and the anti-TNF- α compound is Enbrel or Remicade.

46. A method of treating multiple sclerosis which comprises co-administration one or more compounds selected from Avonex, Betaseron, Copaxone or other compounds indicated for the treatment of multiple sclerosis and one or more compounds of Claim 1.
15

47. A method of treating multiple sclerosis which comprises co-administration one or more compounds selected from Avonex, Betaseron, Copaxone or other compounds indicated for the treatment of multiple sclerosis and one or more compounds of Claim 7.
20

48. A composition for treating multiple sclerosis which comprises one or more compounds selected from Avonex, Betaseron, Copaxone or other compounds indicated for the treatment of multiple sclerosis and one or more compounds of Claim 1.
25

49. A composition for treating multiple sclerosis which comprises one or more compounds selected from Avonex, Betaseron, Copaxone or other compounds indicated for the treatment of multiple sclerosis and one or more compounds of Claim 7.
30

50. A method of treating psoriasis which comprises co-administration of one or more compounds selected from the class consisting of an immunosuppressive, a steroid, an anti-TNF- α compound or other classes of compounds indicated for the treatment of psoriasis and one or more compounds of Claim 1.

5 51. A method of treating psoriasis which comprises co-administration of one or more compounds selected from the class consisting of an immunosuppressive, a steroid, an anti-TNF- α compound or other classes of compounds indicated for the treatment of psoriasis and one or more compounds of Claim 7.

10 52. The method of Claim 50 wherein the immunosuppressive is methotrexate, leflunimide, sulfasalazine or cyclosporin, the steroid is β -methasone and the anti-TNF- α compound is Enbrel or Remicade.

53. The method of Claim 51 wherein the immunosuppressive is methotrexate, leflunimide, sulfasalazine or cyclosporin, the steroid is β -methasone and the anti-TNF- α compound is Enbrel or Remicade.

15 54. A composition for treating psoriasis which comprises one or more compounds selected from the class consisting of an immunosuppressive, a steroid, an anti-TNF- α compound or other classes of compounds indicated for the treatment of psoriasis and one or more compounds of Claim 1.

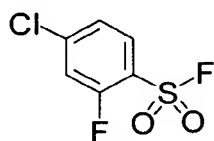
20 55. A composition for treating psoriasis which comprises one or more compounds selected from the class consisting of an immunosuppressive, a steroid, an anti-TNF- α compound or other classes of compounds indicated for the treatment of psoriasis and one or more compounds of Claim 7.

25 56. The composition of Claim 54 wherein the immunosuppressive is methotrexate, leflunimide, sulfasalazine or cyclosporin, the steroid is β -methasone and the anti-TNF- α compound is Enbrel or Remicade.

57. The composition of Claim 55 wherein the immunosuppressive is methotrexate, leflunimide, sulfasalazine or cyclosporin, the steroid is β -methasone and the anti-TNF- α compound is Enbrel or Remicade.

reaction mixture was cooled to 0 °C and a solution of NaNO₂ (27.2 g, 0.4 mol) dissolved in 40 mL of H₂O was added over 10 min. The reaction mixture was stirred for 30 min at 0 °C. In a separate flask, 500 mg of CuCl was dissolved in 200 mL of AcOH. The flask was cooled to 0 °C and SO₂ gas was bubbled into the solution for 40 minutes. The contents of the "aniline" flask were added to the contents of the second flask over 20 minutes causing a vigorous evolution of gas. After the addition was complete, the ice bath was removed, and the reaction mixture was allowed to warm to rt. The reaction mixture was poured into 500 g of chipped ice and the resulting solids were collected, washed and dried to give 26.1 g (73%) of compound 53.

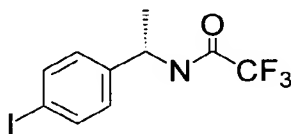
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Compound 54

Compound 54. Compound 53 (4.0 g, 17.5 mmol) was dissolved in acetone (80 mL) and a solution of potassium fluoride (2.03 g, 35 mmol) in water (40 mL) was added. The reaction mixture was stirred at rt overnight. It was partially concentrated on the rotovap, then partitioned between CH₂Cl₂ and water. Evaporation of the solvent afforded Compound 54 (2.60 g, 70%) as an oil.

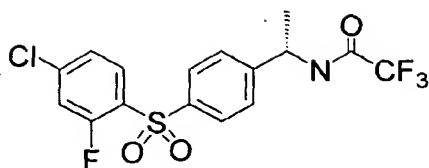
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Compound 55

Compound 55. Compound 55 was prepared from α-methyl benzylamine using a procedure similar to that used to prepare compound 1. N-Iodosuccinamide was substituted for DBDMH and the product was recrystallized from isopropanol/water.

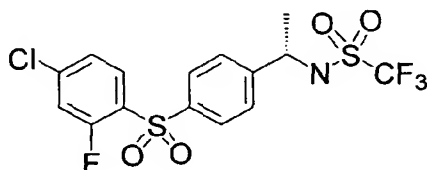
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Compound 56

Compound 56. Compound 55 (4.33g, 12.5 mmol) was dissolved in THF (50 mL) and TMEDA (5.6 mL, 37 mmol) was added. The flask was placed under N₂ blanket and cooled to 0 °C. A solution of isopropyl magnesium chloride (2.0 M in THF, 15 mL, 30 mmol) was added via syringe over 6 min. The reaction mixture was stirred at 0 °C for 1 h. The resulting solution was transferred via cannula into a flask containing compound 53 (15 mmol) in an ice-water bath over 15 min. The reaction mixture was left stirring at 0 °C for 1.5 h. Aq NH₄Cl was added and the reaction mixture was extracted with EtOAc. The combined organic layer was washed with brine and dried with MgSO₄. The solvents were evaporated and the crude product was purified via sgc using 1:4 EtOAc/Hexanes as the mobile phase. Solid compound 56 (3.5 g, 68%) was obtained.

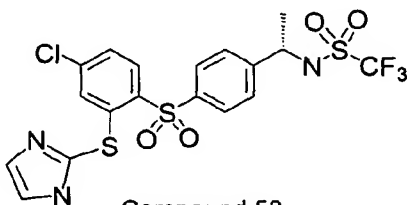
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Compound 57

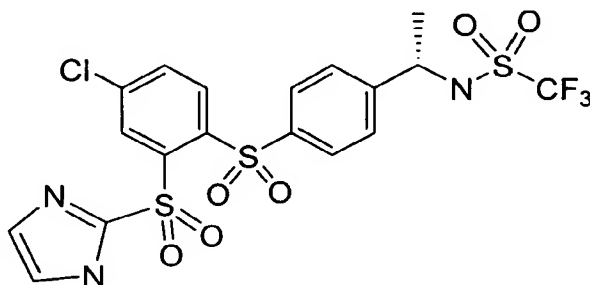
Compound 57. Compound 56 was converted to compound 57 using hydrolysis and sulfonylation procedures similar to those described in Example II.

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Compound 58

Compound 58. Compound 57 (0.10g, 0.22 mmol) was dissolved in 1 mL of dioxane and 2-mercaptoimidazole was added (28 mg, 0.28 mmol). Sodium hydride (60% dispersion in mineral oil, 18 mg) was added and the reaction mixture was stirred at 100 °C for 8 h. The reaction mixture was quenched with ice and extracted with EtOAc. The organic layer was dried with MgSO₄ and the solvents were evaporated. The crude product was purified via sgc using a 5:95 MeOH/CH₂Cl₂ mobile phase to give 18 mg (15%) of compound 58 as product.



Compound LVII

Compound LVII. Compound 57 was oxidized to compound LVII using a procedure similar to that used to oxidize Compound XIX to compound XXI.

It will be understood that various modifications may be made to the embodiments and examples disclosed herein. Therefore, the above description should not be construed as limiting, but merely as exemplifications of preferred embodiments. Those skilled in the art will envision various modifications within the pe and spirit of the claims appended hereto.